REMARKS

Claims 1-9 and 12-20 are pending in this application.

Claims 10 and 11 have been canceled.

Claims 5-7 and 14-20 have currently been withdrawn.

Claim 1 has been amended to provide values for n1, n2 and n3 and to recite alamine or valine as X4. Support for the amendment can be found in the Specification on page 12, lines 18-30.

Claim 2 has been amended to recite alanine as X4.

No new matter has been added.

Rejections Under 35 USC § 112, Second Paragraph

The Examiner has rejected claims 1-4, 8, 9, 12 and 13 as indefinite for failing to recite a definition of variables n1, n2 and n3. Applicants have added definitions for these variables, thereby overcoming the rejection.

The Examiner has also rejected claims 1-4, 8, 9, 12 and 13 as confusing for the recitation of "LINKER eventually absent represents a chemical link between PEPTIDE and SIGNAL." Applicants have deleted the phrase "eventually absent" from the claim, thereby overcoming the rejection.

Rejections Under 35 USC § 103

The Examiner has rejected claims 1-4, 8, 12 and 13 as obvious over Carpenter in view of Odake, and/or Odake and Portet . The Examiner's comments on pages 6-9 of the Office Action are lengthy and are not repeated here. To summarize, the Examiner contends that Carpenter discloses MRI contrast agent comprising matrix metalloproteinase inhibiting targeting moieties attached to one or more paramagnetic metal ions having an optional linking moiety, L_n, between the targeting moieties and the paramagnetic metal ions. The Examiner admits, however, that Carpenter does not specifically recite that hydroxamic tetrapeptide derivatives such as p-aminobenzoy-Gly-Pro-D-Leu-D-Ala-NHOH [sic] is used as the MMP targeting ligand.

With regard to Odake, the Examiner contends that this reference discloses peptide derivatives having specific inhibitory activity against collagenases and that abnormal overaction of collagenases is shown in processes of destruction and repair of tissues, so that inhibition of collagenases provides a useful means for treating such diseases. The Examiner notes that p-aminobenzoy-Gly-Pro-D-Leu-D-Ala-NHOH is disclosed.

As for Portet, the Examiner contends that this reference discloses iron oxide nanoparticles as contrast agents in magnetic resonance imaging.

From this the Examiner concludes that a skilled artisan would have used the hydoxamic acid tetrapeptide derivatives of Odake as an MMP inhibitor (Q) in the compounds and method of Carpenter. The Examiner states that it would have been obvious to substitute the as p-aminobenzoy-Gly-Pro-D-Leu-D-Ala-NHOH as a functional equivalent of succinyl hydroxamates and alanine hydroxamates as inhibitor disclosed by Carpenter; in essence that the skilled artisan could have substituted one known MMP (collagenase) inhibitor for another and that the results of the substitution would have been predictable. Applicants respectfully traverse.

Applicants first note that the problem to be solved was to find specific targeting ligands capable of effectively targeting MMP in vivo. Applicants respectfully submit that the Examiner's rejection appears to be the result of hindsight that has arisen by piecing together some logic using the disclosure of the instant Specification, which provides the technical solution to the problem to be solved. Applicants submit that the skilled artisan would not have contemplated using the peptides described in Odake, and having a reasonable expectation of success in so doing, for at least the following reasons.

1. A huge number of potential MMP targeting entities exist

Because there are a very large number of potential MMP targeting entities it would not have been obvious to select the peptides of the invention and to then expect, with a reasonable chance of success, that these particular peptides would solve the problem of finding specific targeting ligands capable of effectively targeting MMP in vivo.

Indeed, there is a very large gap between the theoretical affinity of a MMP ligand (biovector) in vitro and its real and actual efficiency in vivo. This occurs for many reasons, such as loss of affinity, loss of efficiency, loss of stability, etc. This is clearly mentioned on page 4, line 22 to page 5, line 10 of the instant application and is supported in the literature; see, for example, Annals of the New York Academy of Sciences (1999) 878:413-419 (abstract attached).

2. It was not obvious to believe that the affinity of the peptide toward the MMP would be preserved in the tissue

Once coupled to a signal entity, such as a chelate moiety or iron oxide particles, many MMP peptidic inhibitors have drastically altered affinity/efficiency. Surprisingly, the strong efficiency (affinity and selectivity) of the compounds of the instant invention is clearly demonstrated in vivo (e.g. mouse experiments) and ex-vivo on humans. The attached published articles conclude that P947, which is a compound according to the present invention, is a very promising product for human diagnostic imaging.

3. Odake describes only the therapeutic use of these peptides and does not describe or suggest their use in the imaging diagnostic field.

The Odake reference is focused on the therapeutic use of peptides and does not suggest their use for imaging diagnostics.

4. It was further surprising that the product according to the instant invention would be effectively efficient in view of the very low level of MMP target

According to the prior art at the time of filing,

- the MMP concentration in the targeted atherosclerotic tissue (atheroma plaque) was about 50 nM
- this very weak quantity could normally not have been detected by MRI with the relaxivity level of the compound used in the present invention (about 5mM-1 Gd-1s-1): indeed according to the common knowledge in the MRI

> field at the time the application was filed, the sensitivity of MRI should not have been able to allow the imaging of a biological target at a concentration of less than about 10μM to 1 mM. That is, the MMP concentration in the targeted atherosclerotic tissue was at least twenty fold less than the amount which could normally be detected.

In other words, in using the compounds according to the present invention, either no MRI signal or only a non-MMP specific signal should have been obtained.

Several experiments giving clear evidence of such MMP specific signal have been carried out using the compounds according to the present invention in which the signal entity is DOTA-Gd, such as the above-mentioned in vivo mouse experiments and the ex vivo rabbit and human experiments described in the instant application on pages 25-30 and in Figure 1 (compound B/P947). These experiments provide data which demonstrate the effectiveness of the presently claimed compositions for the purposes recited in the present claims which could not be predicted in view of the prior art.

This is also clearly indicated in the article of Lancelot et al. on page 429, first column, at the end of the first paragraph of the discussion part, which states "the coupling with the contrast moiety did not alter the properties of the peptides." Furthermore, while the signal entity used for P947 is DOTA-Gd and not USPIO, the P947 peptide used in the study is the same as instant compound B.

In view of the above, Applicants submit that one of skill in the art would not have had a reasonable expectation of success in combining the prior art references to obtain the instant invention. Consequently, Applicants request removal of the rejection and allowance of the claims.

Conclusion

In view of the above remarks, all of the claims are submitted as defining non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested. Applicant believes the pending application is in condition for allowance.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $1,110.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Andrew D. Meikle, Registration No 32,868, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: September 10, 2010

Respectfully submitted,

#47,604

By _____
Andrew D. Meikle
Registration No.: 32,868
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant

Attachment: Annals of the New York Academy of Sciences